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Covid-19 in Hospitalized Patients with Type 2 Diabetes Treated by Metformin: A Systemic Review and Retrospective Analysis

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ABSTRACT

Objectives: Metformin is a widely prescribed oral antihyperglycemic agent used as first line therapy for type 2 diabetes mellitus. Therefore, there has been growing interest in the role of metformin in treating various inflammatory conditions. The aim of this analysis is to determine whether treatment with metformin is associated with lower mortality in those infected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Method: A single-center retrospective study, carried out at the 5th Department of Internal Medicine in University Hospital in Bratislava. A total of 133 diabetic patients hospitalized with confirmed COVID-19, from 14th November 2020 to 7th May 2021, were grouped into metformin and no-metformin groups according to the diabetic medications used prior to hospitalization. The demographics, characteristics, laboratory parameters, treatment and clinical outcome in these patients were retrospectively assessed.

Results: Age and chronic microvascular complications of diabetes were significant risk factors for the mortality of COVID-19. There was no difference in the type of oxygen therapy, blood count and inflammatory markers in blood among patients taking metformin prior to hospitalization and patients with other antidiabetic treatments.

Conclusion: The analysis showed that metformin treatment was not associated with lower mortality, thus justifies the implementation of prospective studies to understand the mechanism and causality.

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Introduction

COVID-19 is a pandemic of unprecedented proportions in recent human history. There have been massive efforts geared towards finding safe and effective medications. Despite exponential growth in COVID-19-related research, better understanding of this highly contagious and lethal virus is needed. One of the major risks of COVID-19 infection is the concomitant decompensation of comorbidities. For diabetic patients, a febrile disease represents an excessive burden, which is associated with hyperglycemia despite lack of appetite, also potentiated by increased secretion of counterregulatory hormones and reduced physical activity. Delayed intervention threatens the development of diabetic ketoacidosis and hyperglycemia are usually accompanied by dehydration. Unchanged dosage of oral antidiabetic drugs and insulin in this case poses risk of hypoglycemia.

Metformin is the first-line medication for type 2 diabetes (T2D) [1]. Recent studies show that metformin not only ameliorates chronic inflammation by improving metabolic parameters but also has a direct anti-inflammatory effect. Considering these findings, it is essential to identify the inflammatory pathways targeted by metformin to develop a comprehensive understanding of the mechanisms of action of this drug. The objective of this analysis is to investigate the association between metformin treatment and mortality rates in individuals infected with SARS-CoV-2.

Materials and Methods

A systematic literature search was conducted for the review on metformin, utilizing the following databases: PubMed, Embase, Scopus, and the Directory of Open Access Journals. The search strategy employed combinations of relevant keywords, including "diabetes mellitus," "metformin," "inflammation," "COVID-19," and "mortality."

A retrospective analysis was carried out at the 5th Department of Internal Medicine in University Hospital in Bratislava. The enrolled patients were hospitalized from 14th November 2020 to 7th May 2021. Patients met all the following inclusion criteria:

- Pneumonia associated with COVID-19 was the primary diagnosis on admission
- Positive reverse transcription polymerase chain reaction test for SARS-CoV-2
- Type 2 diabetes mellitus.

Therapeutic management was implemented in accordance with internal recommendations for the treatment of the disease COVID-19 at the University Hospital in Bratislava. Patients who were treated with metformin prior to hospitalization received daily dosages ranging from 500 mg to 2000 mg. Upon admission the metformin treatment was discontinued because the risk of developing lactic acidosis and renal insufficiency. During hospitalization in our department, patients had their blood glucose levels corrected by subcutaneous insulin. Laboratory parameters were determined using standard commercial laboratory sets. The sample consists of 133 patients, of which 74 were men and 59 were women, representing 55.6% and 44.4% of the entire sample. In terms of age, the sample reached an average of 68.78 years. The youngest respondent was 33 years old and the oldest 89 years old.

All routine medications prescribed before hospitalization were identified from admission records, medical files, and, when necessary, by contacting the patient's general practitioner.

Statistical Analysis

For data analysis, given the established hypotheses and the nature of the data, we used the Chi-square test, Kolmogorov-Smirnov normality test, T-test for 2 independent samples and Mann-Whitney U-test for two independent selections. We used each of these tests for individual hypotheses in accordance with the nature of specific data appearing in the given hypothesis. The level of significance was regarded as p value < 0.05.

Glucose-Lowering Effect of Metformin

Multiple mechanisms have been proposed to explain the hypoglycemic action of metformin. However, its principal effect is the reduction of hepatic glucose output, primarily resulting from the inhibition of gluconeogenesis [2]. Metformin also enhances glucose uptake in muscle [3]. A significant hypothesized target of metformin is AMP-activated protein kinase (AMPK), a cellular metabolic sensor that is activated under conditions of metabolic stress. AMPK is a major cellular regulator of lipid and glucose metabolism. Activation of AMPK leads to several metabolic effects: inhibition of hepatic glucose production, improved insulin sensitivity, muscle glucose uptake and increased fatty acid oxidation [4]. The mammalian target of rapamycin (mTOR), a kinase vital for cellular growth and protein synthesis, is a major downstream target of AMPK [5]. Metformin induces AMPK activation in a dose- and time-dependent manner, characterized by a reduction in adenosine triphosphate (ATP) levels and a concomitant elevation in adenosine monophosphate (AMP) concentration. However, evidence also suggests that metformin can stimulate AMPK activity independent of alterations in the AMP/ATP ratio, potentially through the inhibition of mitochondrial respiratory chain complex I and the generation of reactive nitrogen species (RNS) [6]. Conversely, Foretz et al. reported that metformin exhibited a comparable hypoglycemic effect in mice deficient in hepatic AMPK and in wild-type controls. These findings suggest that the suppression of hepatic glucose output by metformin is independent of AMPK activity [7]. Within murine hepatocytes, metformin promotes the accumulation of AMP and related nucleotides. This accumulation results in the inhibition of adenylate cyclase, leading to diminished cyclic AMP levels and reduced protein kinase A (PKA) activity. Consequently, the phosphorylation of critical PKA substrates is abolished, thereby inhibiting glucagon-stimulated glucose output from hepatocytes [8]. Madiraju et al. have suggested an alternative mechanism by which metformin suppresses gluconeogenesis, namely, through the inhibition of mitochondrial glycerophosphate dehydrogenase [9]. Although the complete molecular mechanism of metformin's action is not fully understood, the drug primarily lowers blood glucose by suppressing glucose production in the liver.

Anti-Inflammatory Effect of Metformin

Mechanism

Metformin restores endothelial function and elicits significant improvements in nitric oxide (NO) bioavailability, with concomitant reductions in glycation and oxidative stress, in both normal and high-fat-fed rat models. This study found that metformin treatment significantly increased NO bioavailability and decreased glycation, oxidative stress, and levels of the chemokine CCL2 (monocyte chemoattractant protein-1) in the aorta [10]. Metformin has also been reported to enhance NO synthesis through AMPK activation [11]. In bovine aortic endothelial cells, metformin has been shown to both enhance NO synthesis through AMPK activation and reduce reactive oxygen species (ROS) production via inhibition of NAD(P)H oxidase and the mitochondrial respiratory chain [12]. A separate study demonstrated that in high-fat-fed atherogenic rabbits, metformin inhibited nuclear factor κB (NFκB) activation within the vessel wall and decreased serum levels of C-reactive protein (CRP) [13]. Hattori et al., using human umbilical vein endothelial cells, demonstrated that metformin attenuates cytokine-induced nuclear factor κB (NFκB) activation via the activation of AMPK [14]. An additional potential mechanism underlying the anti-inflammatory action of metformin is the inhibition of advanced glycation endproduct (AGE) formation. AGEs are known to promote inflammation and ROS generation (glycoxidation). Therefore, their inhibition by metformin contributes to its anti-inflammatory properties [15,16]. Hyperglycemia enhances the formation of AGEs. Metformin relieves this process by reacting chemically with dicarbonyl precursors of AGEs, such as methylglyoxal, thereby reducing their concentration. Furthermore, metformin inhibits AGEs-induced apoptosis, inflammatory responses, and fibrotic reactions in renal tubular cells. This protective mechanism is mediated by a reduction in ROS generation, resulting from the suppression of receptor for AGEs (RAGE) expression via AMPK activation [17]. The anti-inflammatory action of metformin is not limited to vascular endothelial cells and smooth muscle cells but extends to other cell types. Specifically, it has been demonstrated that metformin diminishes the production of NO, prostaglandin E2, and pro-inflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) in macrophages through the inhibition of NFκB activation [18]. The finding that metformin suppresses ROS and allergic eosinophilic inflammation via AMPK activation in mouse lung tissue suggests that it may offer a new pharmacological approach to managing asthma [19]. In a non-diabetic mouse model of nonalcoholic steatohepatitis, Kita et al. reported that metformin both prevented and reversed steatosis and inflammation. However, this effect seemed to be independent of AMPK activation [20]. The indirect anti-inflammatory action of metformin is associated with its metabolic consequences. Amelioration of hyperglycemia and induction of weight loss following metformin treatment exert favorable effects on chronic inflammation and atherogenesis.

Clinical Studies

The United Kingdom Prospective Diabetes Study (UKPDS) trial demonstrated that metformin treatment significantly lowered the risk of diabetes-related death and adverse outcomes in overweight patients with T2D compared to dietary intervention or treatment with sulfonylurea or insulin. The reduced risk included events of atherosclerotic cardiovascular disease, a condition in which

chronic, low-grade inflammation is a significant contributing factor. This led to the later hypothesis that metformin's anti-inflammatory properties might partially account for its observed clinical benefits [21]. The Hyperinsulinemia: the Outcome of its Metabolic Effect (HOME) trial randomized 390 insulin-treated patients with T2D to either metformin or placebo. Sixteen weeks of metformin treatment resulted in improved blood plasma markers of endothelial function; however, there was no observed decrease in CRP, a parameter of inflammation [22]. A significant finding from the long-term follow-up of the HOME trial was a decrease in the secondary composite macrovascular endpoint in patients treated with metformin [23]. A study involving patients with T2D found that four weeks of metformin treatment reduced levels of plasminogen activator inhibitor-1 and leptin but did not affect CRP levels. This suggests that metformin may have effects on adipose tissue [24]. A crossover study comparing metformin and the insulin secretagogue repaglinide in non-obese patients with T2D was conducted. Despite achieving comparable glycemic control in both treatment arms, metformin administration resulted in a significant reduction in TNF-α and soluble intercellular adhesion molecule-1 levels, without significant alterations in CRP or IL-6 levels [25]. In a randomized controlled trial, the effects of metformin were compared with those of the thiazolidinedione, rosiglitazone. After 12 weeks of treatment, serum concentrations of IL-6 and TNF-α were significantly reduced in both groups relative to baseline, but no statistically significant difference was observed between the metformin and rosiglitazone groups [26]. Another clinical trial compared the effects of the α-glucosidase inhibitor acarbose and metformin on inflammatory parameters over a one-year treatment period. While both treatment groups exhibited significant reductions in TNF-α and IL-6 levels compared to baseline, no significant alterations were observed in interleukin-2 (IL-2) or IL-1β levels. Furthermore, there were no statistically significant differences between the acarbose and metformin groups [27]. Placebo-controlled studies in patients with prediabetes who were also taking lipid-lowering drugs have demonstrated anti-inflammatory effects of metformin. In one such study, individuals with impaired fasting glucose already receiving simvastatin were randomized to either placebo or 3 grams of metformin daily. After 90 days the metformin group experienced reduced plasma levels of CRP and decreased lymphocyte release of IL-2, interferon-γ (IFN-γ) and TNF-α [28]. An open-label study involving overweight individuals with impaired glucose tolerance compared the effects of simvastatin and metformin. Half the participants received simvastatin, and the other half received metformin. After 16 weeks of treatment, both groups exhibited significant reductions in CRP and IL-6 levels compared to baseline values. However, there were no significant changes in TNF-α levels, and no other significant differences between the two treatment groups [29]. A study of T2D patients showed that metformin significantly lowered serum CRP levels compared to placebo, along with reducing oxidative and nitrosative stress [30].

In conclusion, metformin's potent effects on mitochondrial function, autophagy, and immune modulation significantly impact inflammation. This antidiabetic drug's versatility is evident in its effects on multiple cellular processes, demonstrating its relevance to human health beyond blood glucose control.

Cardiovascular Protective Effects of Metformin

The UKPDS revealed that metformin reduced macrovascular complications independently of its glucose-lowering effect. The risk of developing nonfatal myocardial infarction (MI) in patients with diabetes mellitus was reduced by 39% with metformin therapy [21]. Even in the 10-year post-trial follow-up of UKPDS survivors, metformin's protective effects remained evident [31]. A large, double-blind, randomized controlled trial evaluated the cardiometabolic effects of metformin in overweight or obese adult patients with diabetes and elevated cardiovascular disease (CVD) risk. The study demonstrated reductions in body weight, low-density lipoprotein (LDL) cholesterol, and the progression of atherosclerosis, as assessed by carotid artery intima-media thickness, a marker for CVD [32]. The beneficial cardiac effects of metformin have been observed in patients with and without pre-existing heart failure. In individuals without diabetes who had experienced MI, twelve weeks of metformin treatment resulted in reduced left ventricular dilation, improved left ventricular ejection fraction, and decreased levels of atrial natriuretic peptide. These findings suggest that metformin may attenuate cardiac remodeling and slow the progression to heart failure following an MI [33]. In diabetic rat models, metformin treatment results in decreased superoxide production and reduced accumulation of AGEs within the vasculature. Furthermore, levels of monocyte chemoattractant protein-1, an early molecular marker of vascular inflammation in atherogenesis, are significantly attenuated in the aortic tissue. Additionally, metformin antagonizes vascular inflammation by inhibiting the differentiation of monocytes into macrophages, a process that critically accentuates atherosclerosis through the promotion of a pro-inflammatory environment within the vessel wall [10]. Clinically, three randomized controlled trials are providing the most important evidence of the cardiovascular protective effects of metformin, including UKPDS and two prospective clinical trials carried out by Kooy et al. in 2009 and Hong et al. in 2013. The second clinical trial observes that adding metformin to insulin did not improve the primary endpoint (a composite of microvascular and macrovascular morbidity and mortality) in T2D patients, a 4.3-year follow-up revealed a reduced risk of macrovascular disease [23]. A third clinical trial compared glipizide and metformin regarding their long-term effects on major cardiovascular events in patients with T2D and a history of coronary artery disease. The results showed that three years of metformin treatment significantly reduced the incidence of major cardiovascular events compared to glipizide, after a median follow-up period of five years [24].

Therapeutic Potential of Metformin in Covid-19

A fascinating characteristic of metformin is its antimicrobial activity, which has been demonstrated in various preclinical models. These models include infections with Mycobacterium tuberculosis, Staphylococcus aureus, Zika virus, and dengue virus [37]. Several antihyperglycemic agents are routinely employed to manage blood glucose levels in patients with diabetes. A crucial question remains regarding the optimal selection of an antihyperglycemic medication, in conjunction with other necessary therapies such as antivirals, to effectively control blood glucose, reduce the risk of long-term post-COVID-19 sequelae, and ultimately improve survival outcomes in diabetic patients infected with SARS-CoV-2. Virus enters the human body through the interaction between its spike protein and the N-terminal part of ACE2 (Angiotensin-Converting Enzymes 2). Metformin works through the activation of AMPK, which leads to phosphorylation of ACE2. In theory, this addition of a phosphate group would cause conformational and functional changes in the ACE2 receptor. This could lead to a reduced binding capacity for SARS-CoV-2, due to spherical blockage by adding a large molecule. However, once the virus is inside a cell, ACE2 receptors are downregulated. This leads to a disbalance in the renin-angiotensin-aldosterone system (RAAS), which has harmful pro-inflammatory and profibrotic effects. By upregulating ACE2, the imbalance in the RAAS

could be reversed. Metformin should therefore not only prevent the entry of SARS-CoV-2 as described above, but also suppress the harmful consequences by causing ACE2 activation through AMPK signaling [38]. A significant association between metformin treatment and reduced COVID-19-related mortality has been reported in meta-analysis studies [39,40]. As well retrospective studies suggest that metformin treatment significantly reduces mortality in high-risk diabetic patients with COVID-19 [41]. A retrospective cohort study, encompassing 6,256 participants with type 2 diabetes or obesity and COVID-19, identified a gender-specific effect of metformin. Among the subgroup of 2,333 patients receiving metformin prior to their COVID-19 diagnosis, a significant association was observed between metformin treatment and reduced disease severity and mortality in women, but not in men [42]. Another retrospective study analyzing 1,213 patients with COVID-19, including 678 patients receiving metformin, demonstrated an association between metformin treatment and an increased incidence of acidosis, but not mortality, in the subgroup of patients with type 2 diabetes. The incidence of acidosis was positively correlated with higher metformin dosage, compromised renal function, and greater severity of COVID-19 illness [43]. Crouse et al. confirmed the role of diabetes mellitus as a significant independent risk factor contributing to elevated mortality rates among COVID-19 patients compared to non-diabetic individuals. Their study reported a threefold reduction in mortality among diabetic COVID-19 patients receiving metformin prior to their COVID-19 diagnosis, while prior insulin use demonstrated no significant effect on mortality. This beneficial effect of metformin remained statistically significant after adjusting for other established COVID-19 risk factors, including age, sex, race, obesity, hypertension, chronic kidney disease CKD and heart failure [44].

The results of prior relevant investigations into the association between metformin use and mortality in COVID-19 patients are displayed in Table 1. Multiple studies of outpatients have demonstrated that metformin use is associated with a lower risk of serious COVID-19 outcomes, including hospitalization and death [42,44,45]. No significant influence of metformin treatment was seen in other studies [46,47-49]. Additionally, Table 1 provides a summary of mortality from retrospective studies conducted on patients admitted to hospital with COVID-19 [42,43,50-52]. The majority of these studies reported improved clinical outcomes in cohorts of patients receiving metformin versus those not receiving it. These improvements included reductions in mortality, decreased need for high-intensity treatment (e.g., intensive care unit admission or mechanical ventilation), and a lower incidence of acute respiratory distress syndrome. Cheng et al. reminds a greater incidence of acidosis (including lactic acidosis) was observed in metformin users compared to non-users; however, mortality was not affected, and there was an apparent decrease in the frequency of heart failure among those taking metformin [43]. A potential cause of the increased acidosis risk is the accumulation of excess plasma metformin due to the rapid deterioration of renal function seen in more than fifth of patients with severe COVID-19 [53]. Acute renal failure is a contraindication for metformin use, necessitating its discontinuation, as will be discussed subsequently. A small study comprising 110 subjects reported an increased incidence of life-threatening COVID-19 complications associated with metformin treatment during the hospital stay [54].

Majority of the aforementioned studies reported either no effect or a potential benefit associated with pre-existing metformin treatment on clinical outcomes following COVID-19 infection. However, the retrospective nature of these data limits their applicability to guiding future clinical practice.

Table 1: Overview of Retrospective Studies of Metformin's Effect in Patients Infected by Covid-19

Reference	Subjects	OR (95% CI)	Summary
Studies in outpatiens			
Wang J. et. Al. 2021	10,183 metformin users vs. 10,183 non-metformin users (propensity score-matched cohorts)	0.87 (0.34 – 2.20)	No effect on mortality
Crouse et al. 2020	76 metformin users vs. 144 non-metformin users	0.33 (0.13 – 0.84)	Reduced mortality
Bramante et al. 2020	676 metformin users vs. 8,879 non-metformin users	0.32 (0.15 – 0.66)	Reduced mortality, hospitalization, ICU
Oh and Song, 2021	5946 metformin users vs. 5946 non-metformin users (propensity score-matched cohorts)	1.26 (0.81 – 1.95)	No effect on mortality
Ghany et al. 2021	392 metformin users vs. 747 non-metformin users	0.34 (0.19 – 0.59)	Reduced mortality, hospitalization, ARDS
Lally et al. 2021	127 metformin users vs. 476 non-metformin users	0.48 (0.28 – 0.84)	No effect on mortality
Do et al. 2021	469 metformin users vs. 95 non-metformin users	0.77 (0.44 – 1.35)	No effect on mortality
Patients hospitalized for COVID-19			
Cheng et al. 2020	678 metformin users vs. 535 non-metformin users	1.65 (0.71 – 3.86)	No effect on mortality
Lalau et al. 2021	1,496 metformin users vs. 953 non-metformin users	0.71 (0.537 – 0.938)	Reduced mortality, tracheal intubation
Wargny et al. 2021	782 metformin users vs. 2012 non-metformin users	0.65 (0.45 – 0.93)	Reduced mortality
Jiang et al. 2021	100 metformin users vs. 228 non-metformin users	0.48 (0.13, 1.74)	No effect on mortality and severity. Reduced risk of ARDS
Bramante et al. 2021	2,333 metformin users vs. 3923 non-metformin users	0.887 (0.782 – 1.008)	No effect on overall mortality, reduced mortality in women but not in men

Results

Chronic microvascular complications of diabetes (diabetic nephropathy, neuropathy, and retinopathy) were more prevalent in non-survivors compared with survivors (p=0.0002). Furthermore,

severe and fatal courses are associated with elderly age (<0.0001). Gender, BMI and type of diabetes treatment were not identified as risk factors for death due to COVID-19. (see Table 2)

Comparing the patients treated by metformin prior to hospitalization to patients who used any other diabetes therapy, there were no statistically significant differences in blood count (number of leucocytes, neutrophils, lymphocytes, platelets), inflammatory markers (CRP, procalcitonin (PCT), D-dimer, IL-6), renal parameters (urea, creatinine) or type of oxygen therapy (low-flow, high-flow) during hospital stay. (see Table 3)

Table 2: Basic Demographic, Clinical and Laboratory Characteristics

	Survivors (n=69)	Non-survivors (n=64)	P value
Gender (Men, Women) n (%)	40(58)/29(42)	34(53)/30(47)	0.574
Age	64.59±12.6	73.3±8.52	< 0.0001
BMI	31.49±8.53	32.94±7.58	0.153
Chronic complications of diabetes (No, Yes) n (%)	46(67)/23(33)	22(34)/42(66)	0.0002
Oral hypoglycemic agents (No, Yes) n (%)	27(39)/42(61)	22(34)/42(66)	0.57
Use of metformin (No, Yes) n (%)	33(48)/36(52)	34(53)/30(47)	0.541
Use of insulin (No, Yes) n (%)	60(87)/9(13)	49(77)/15(23)	0.119

Table 3: Comparison of Patients with and without Metformin

	Patients without metformin (n=67)	Patients with metformin (n=66)	P value
Low-Flow oxygen therapy			
(No, Yes) n (%)	12(18)/55(82)	11(17)/55(83)	0.85
High-Flow oxygen therapy			
(No, Yes) n (%)	32(48)/35(52)	33(50)/33(50)	0.796
Leukocytes	8.72±4.32	7.87±2.81	0.546
Neutrophils	7.33±4.13	7.74±10.1	0.571
Lymphocytes	0.95±0.55	1.09±1.26	0.423
Platelets	261.03±103.63	246.09±98.56	0.396
CRP	121.84±81.33	136.55±80.72	0.297
IL-6	179.84±584.18	150.78±348.42	0.486
Procalcitonin	2.89±13.12	1.1±4.84	0.88
Glycemia	13.4±9.32	14.11±6.53	0.178
Urea	12.58±8.68	11.09±6.96	0.578
Creatinine	145.73±108.64	128.31±93.05	0.658
D-dimer	2.97±4.37	2.64±4.5	0.094

Discussion

Although important data regarding COVID-19 were gathered with remarkable speed, many aspects of the viral infection's contribution to disease pathogenesis and variable severity among individuals remain to be discovered. It is evident, that hyperglycemia and diabetes-associated comorbidities are significant contributors to increased disease severity and mortality in patients with COVID-19. The antidiabetic agent metformin, beyond its well-known glucose-lowering capabilities, possesses potential antiviral, cardioprotective, immunomodulatory and anti-inflammatory properties, suggesting its potential as a COVID-19 treatment. Diabetes has been recognized as one of the major comorbidities adversely affecting COVID-19 outcome. However, pre-existing metformin use is associated with a substantial reduction in this risk, raising the possibility of a protective effect of metformin in this high-risk population [44]. On the other hand, our findings agree with Bramante et al.'s observational study of over 6,000 US patients with T2D hospitalized for COVID-19, which also found no effect of metformin on in-hospital mortality. In contrast to the lack of effect in men, Bramante et al. found that women taking metformin had lower in-hospital mortality from COVID-19 [42]. The mechanisms by which metformin may improve prognosis in the context of COVID-19 have not yet been identified. Metformin has been shown in numerous studies to improve the energy supply in failing hearts by activating AMPK, a pathway that promotes better use of lipids and glucose [55]. Besides affecting metabolism and energy use, metformin's ability to modulate the immune system may also contribute to its cardioprotective effects [56]. Metformin's effect on ACE2 expression could contribute to its potential protective action against COVID-19. Metformin-mediated activation of AMPK leads to phosphorylation of the ACE2 protein, thereby subsequent degradation [57]. Post-translational modifications of ACE2 could change its structure, reducing the ability of SARS-CoV-2 to attach to the cell surface.

A potential side effect of metformin is lactic acidosis, particularly in cases of hypoxemia or organ failure. Because COVID-19-related ARDS can also cause lactic acidosis, metformin is often avoided in severe or critical COVID-19 cases. Insulin, given subcutaneously or parenterally, is used to manage hyperglycemia in these patients.

The study did not evaluate metformin's impact on COVID-19 outcomes in individuals without T2D. Therefore, the potential for metformin to benefit specific non-diabetic subgroups (such as those with obesity or prediabetes) during COVID-19 infection remains unknown and requires further investigation. It is important to acknowledge that the data were obtained solely from hospitalized patients. Thus, the observed impact of metformin on COVID-19 prognosis in individuals with T2D may not be representative of outcomes in outpatients, or geographically/ethnically diverse cohorts. Moreover, due to the retrospective nature of the study, we could not determine the definitive causal effect between metformin use and the outcomes of the individuals in this study.

Metformin, a safe and affordable drug with a long history of use in type 2 diabetes, holds promise for treating other conditions. Future research, specifically well-designed clinical trials with better patient targeting, will be key to determining its effectiveness, particularly in chronic diseases where inflammation plays a major role.

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